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Wasting of the left ventricle in patients with cardiac cachexia: a cardiovascular magnetic resonance study

Viorel G. Florea[a,b], James Moon[c], Dudley J. Pennell[c], Wolfram Doehner[a,d], Andrew J.S. Coats[a], Stefan D. Anker[a,d,*]

[a] *Department of Clinical Cardiology, Imperial College of Science, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK*
[b] *University of Minnesota, and Veterans Administration Medical Centre, Minneapolis, MN, USA*
[c] *Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London, UK*
[d] *Applied Cachexia Research, Dept. of Cardiology, Charité, Campus Virchow-Klinikum, Berlin, Germany*

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Abstract

Background: The "cachectic heart" has been described as a pathologic decrease in the size and mass of the heart, but no in vivo studies have shown changes in cardiac dimensions or left ventricular (LV) mass over time in chronic heart failure (CHF) associated with body wasting (cardiac cachexia). Cardiovascular magnetic resonance (CMR) has high reproducibility and is more sensitive than other techniques. *Methods:* CMR studies of LV volumes and mass were performed at baseline and a mean of 15 months later in nine CHF patients with cardiac cachexia and 28 matched CHF controls without cachexia (mass index 23 ± 1 vs. 29 ± 5 kg/m^2, $P=0.0005$). *Results:* At baseline, LV end-diastolic volume (197 ± 78 vs. 203 ± 65 ml), end-systolic volume (131 ± 75 vs. 126 ± 63 ml), LV mass (213 ± 44 vs. 222 ± 62 g), and LV ejection fraction (38 ± 19% vs. 40 ± 16%) did not differ between cachectic patients and controls (all $P>0.10$). During follow-up, there was a significant decrease in LV mass in patients with cachexia (−16 g, $P<0.05$) and a trend to increase in LV mass in patients without cachexia (+7 g, $P=0.12$, comparison between groups: $P=0.010$). *Conclusions:* The direction of changes over time in LV mass differs in CHF patients with cachexia as compared with non-cachectic controls. A significant decrease in LV mass occurs in patients with cardiac cachexia. This study documents in vivo the occurrence of wasting of the left ventricle in patients with CHF who demonstrate general body wasting.

Keywords: Heart failure; Cardiac cachexia; Left ventricular mass; Magnetic resonance imaging

1. Introduction

Longstanding severe chronic heart failure (CHF) is often accompanied by a loss of fat, lean and bone mass [1,2], and when the wasting process leads to weight loss it is termed "cardiac cachexia". It has been recognised since the classical description by Hippocrates, and is associated with a particularly adverse prognosis [3]. Although the "cachectic heart" has been described as a pathologic decrease in the size and mass of the heart [4], and although some patients may be shown to lose cardiac mass [5], no study has shown consistent in vivo changes in cardiac dimensions or ventricular mass over time in CHF patients with cardiac cachexia. The purpose of this investigation was to assess prospectively, using highly reproducible cardiovascular magnetic resonance (CMR) techniques, the left ventricular (LV) dimensions, mass and function and the direction and magnitude of changes in these measurements over time in patients with CHF with and without cachexia.

2. Methods

2.1. Patient population and characteristics

The study was performed during the time interval between September 1999 and March 2000. The target population for this study was all cachectic CHF patients (see below for definitions) of ischemic or dilated cardiomyopathy origin, referred for CMR examination as part of their

* Corresponding author. Department of Clinical Cardiology, Imperial College, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK. Tel.: +44-207-351-8203; fax: +44-207-351-8733.
E-mail address: s.anker@imperial.ac.uk (S.D. Anker).

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routine assessment at the Royal Brompton Hospital between April 1998 and May 1999 (index time period). A total of nine consecutive patients with cardiac cachexia were identified physically present at the study time period, with no contraindications for the repeated CMR and willing to participate into the study. These patients (all men, age 50–87 years, duration of heart failure prior to first CMR scan: 10 ± 6 years) had documented non-edematous and non-intentional weight loss of more than 7.5% over a period of more than 6 months prior to the first CMR scan, according to our previous definition of cardiac cachexia [6]. We also aimed to recruit a group of non-cachectic CHF patients of the same age and heart failure etiology to match the cachectic patients in a 1:3 ratio who also had undergone a CMR during the index time period. This group comprised 28 patients with non-cachectic CHF (24 men and four women, age 50–79 years, duration of heart failure prior to first CMR scan: 11 ± 7 years).

The total number of CHF patients who had a CMR scan during the index period was 77 (cachectic: 11 [14%]). Subsequently, three patients died, one patient received a pacemaker, four patients were unstable at the time of being considered for the second study. Three patients declined to participate in the study (no reason stated: two; because of claustrophobia: one). Thus, of 11 patients with cardiac cachexia at the index visit we have restudied nine, and of the remaining 66 non-cachectic patients we have restudied 28. We report on the 37 patients who agreed to participate in the study and had two CMR scans.

The primary end point of the study was the comparison of the changes in LV mass over time between patients with and without cardiac cachexia, on the a priori assumption that non-cachectic patients would demonstrate an increase in LV mass with time, whereas cachectic patients would demonstrate a reduction due to progressive cardiac wasting.

According to our previous findings, CMR requires nine patients with heart failure to detect a 10 g change in LV mass over time with a statistical power of 90% and an α-error of 0.05 [7]. This sample size takes into consideration the intra-observer (2–7%) and inter-study (2–5%) reproducibility of CMR data in patients with CHF, tested in our laboratory [7].

We took the European Society of Cardiology guidelines definition that the diagnosis of heart failure would be made if both of the following were present: symptoms compatible with a diagnosis of heart failure, mainly exertional breathlessness for at least 6 months, and evidence of substantial impairment of LV systolic function or LV filling on Doppler echocardiography [8]. CHF was of ischemic origin in four (44%) cachectic patients and in 14 (50%) non-cachectic patients. The presence of ischemic heart disease was shown either by coronary angiography or documented myocardial infarction. Patients were classified as having dilated cardiomyopathy if normal coronary arteries had been demonstrated on coronary angiography. The cachectic group did not differ significantly from the non-cachectic group with respect to age (69 ± 12 vs. 65 ± 9 years, $P=0.20$), but they demonstrated, as expected, a lower body mass index (23 ± 1 vs. 29 ± 5 kg/m^2, $P=0.0005$).

At the time of investigation, all patients were clinically stable and were regular outpatient attendees. No patients had clinical signs of acute infection or other primary cachectic conditions (such as cancer, thyroid disease, or severe liver disease), none had residual signs of peripheral or pulmonary edema, and were studied when free of ascites. No patients with hemodynamically important valve disease, significant primary pulmonary disease, neuromuscular disorders, myocardial infarction within the previous 6 months, renal failure, peripheral vascular disease, or excessive alcohol intake were included into the study. The medical regimens of all the enrolled patients had been optimised by our heart failure clinic prior to study and they were all symptomatically stable. Standardized medical treatment between the first and second examinations included angiotensin converting enzyme inhibitors (92% of patients), diuretics (97% of patients), nitrates (27% of patients), digitalis (24% of patients), beta-blockers (11% of patients) and aspirin or warfarin (86% of patients) in varying combinations. No significant differences in medication were found between cachectic and non-cachectic patients. The study protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London. All patients gave written informed consent.

2.2. Cardiovascular magnetic resonance

All subjects were imaged using a Picker Edge 1.5 T scanner (Picker, Cleveland, OH, USA). LV volumes were determined by the use of contiguous breath hold short

Table 1
LV dimensions, mass, and ejection fraction in the two groups of patients with and without cachexia at the baseline and follow-up evaluations (mean ± S.D.)

	Visit	Cachectic ($n=9$)	Non-cachectic ($n=28$)	Mean difference	P-value
EDV (ml)	Baseline	197 ± 78	203 ± 65	−6	0.83
	Follow-up	193 ± 86	202 ± 72	−9	0.75
ESV (ml)	Baseline	131 ± 75	126 ± 63	4	0.86
	Follow-up	126 ± 84	129 ± 69	−2	0.93
SV (ml)	Baseline	66 ± 18	76 ± 24	−10	0.25
	Follow-up	66 ± 14	73 ± 22	−7	0.41
EF (%)	Baseline	38 ± 19	40 ± 16	−3	0.67
	Follow-up	41 ± 21	40 ± 16	1	0.92
LV mass (g)	Baseline	213 ± 44	222 ± 62	−9	0.70
	Follow-up	197 ± 36*	229 ± 62	−32	0.16
LV mass/ weight (g/kg)	Baseline	3.30 ± 0.82	2.55 ± 0.69	0.75	0.01
	Follow-up	3.01 ± 0.65*	2.64 ± 0.68†	0.36	0.17

EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; LV mass, left ventricular mass. *$P<0.05$ and †$P=0.10$ between follow-up and baseline examination.

Table 2
Absolute and percent changes in measurements of LV cavity size and mass during the time interval between the baseline and follow-up examinations (mean ± S.E.)

		Cachectic ($n=9$)	Non-cachectic ($n=28$)	Mean difference	P-value
Δ EDV	ml	−4 ± 12	−1 ± 5	−3	0.77
	%	−7 ± 10	−3 ± 3	−4	0.55
Δ ESV	ml	−4 ± 11	2 ± 4	−7	0.44
	%	−21 ± 21	−2 ± 4	−19	0.14
Δ LV mass	g	−16 ± 7	7 ± 4	−23	0.010
	%	−8 ± 3	3 ± 2	−11	0.007
Δ LV mass/ weight	g/kg	−0.29 ± 0.12	0.09 ± 0.05	−0.38	0.002
	%	−8 ± 3	4 ± 2	−12	0.008

Δ, changes over time; EDV, end-diastolic volume; ESV, end-systolic volume; LV mass, left ventricular mass.

axis cines from the mitral valve orifice to the LV apex [9,10]. Care was taken to position the first slice on the atrioventricular valve plane, and subsequent slices were acquired moving towards the apex. Ten to 14 10-mm thick slices were required to cover the ventricle. Imaging time was typically 30 min. The images were analysed using in-house developed software (CMRtools©, Imperial College London, UK). A single independent operator (J.M.) analysed all the images, and he was blinded to the clinical details of the patient and the study date. Although it is not possible to blind the images to body size, the images were presented in random sequence. A fixed set of criteria for the determination of borders was used, and both scans from each patient were analysed side-by-side to minimise inter-study variation [7]. Endocardial and epicardial contours in diastole and endocardial contours in systole were drawn manually and end-diastolic, end-systolic and LV myocardial tissue volumes were calculated by summation. The LV mass was calculated by multiplying the myocardial tissue volume by the myocardial specific density of 1.05 g/cm^3.

2.3. Statistical analysis

Descriptive values are expressed as mean ± S.D. for cross-sectional variables and mean ± S.E. for changes over time within patients groups. A paired Student's t-test, was used to compare the results of the first and second assessments. Differences between group means were compared by unpaired t-test and Mann–Whitney U-test. For all tests, a P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using a standard statistical program package (StatView, version 5.0, Abacus Concepts Inc., Berkeley, CA).

3. Results

A summary of the LV hemodynamic data at the baseline and follow-up examinations for both groups of CHF patients with and without cardiac cachexia is presented in Table 1. By definition, at the baseline examination, the left ventricle was dilated in both groups of patients [9]. At baseline the LVEF was decreased and the LV mass was increased to a similar degree in cachectic and non-cachectic patients, respectively.

During the follow-up period between the two CMR examinations, which averaged 17 months for the cachectic group and 15 months for the non-cachectic group ($P=0.16$), LV dimensions, stroke volume, and ejection fraction showed no significant change in either group of patients (Table 2). In the two study groups blood pressure was similar at baseline ($P=0.5$) and did not change during follow-up ($P>0.2$). Also, body weight remained stable during follow-up

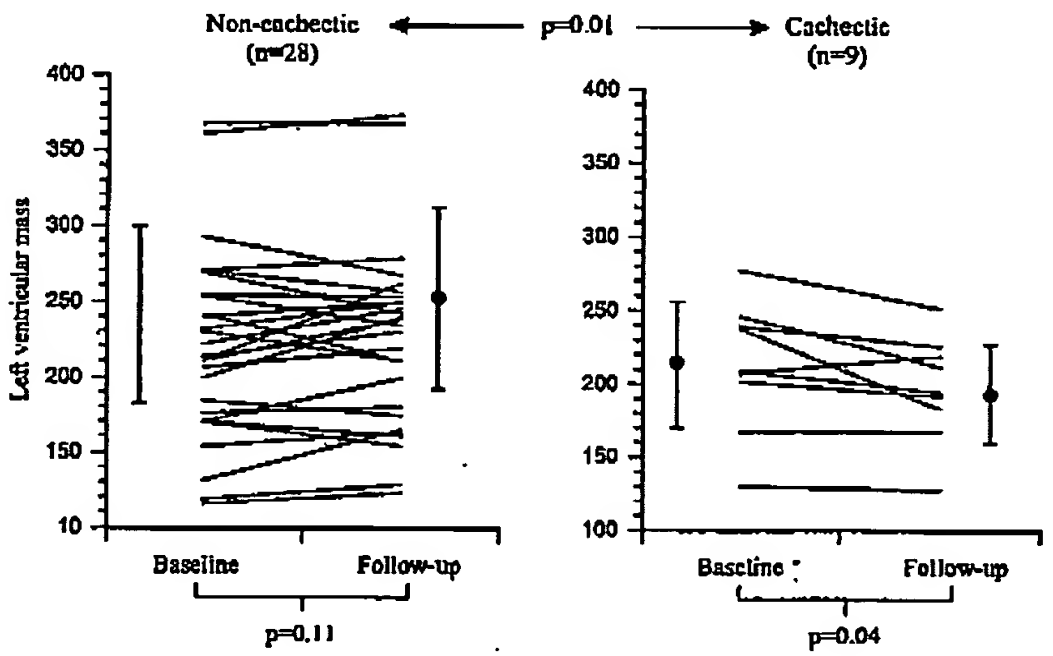

Fig. 1. Change in LV mass from baseline to end of follow-up for patients with and without cachexia. Vertical bars denote 1 S.D. above and below the mean.

(cachectics: 65.3–66.2 kg; non-cachectic patients 87.8–87.6 kg). However, analysing changes over time, we found a significant decrease in LV mass in cachectic patients (-16 ± 7 g, $P=0.04$) and a borderline increase in LV mass in non-cachectic patients ($+7 \pm 4$ g, $P=0.12$). As illustrated in Fig. 1, the direction and magnitude of changes in LV mass over time were significantly different in patients with and without cardiac cachexia ($P=0.010$ for t-test as well as Mann–Whitney U-test).

4. Discussion

The main result of this study is that the syndrome of cardiac cachexia is associated with wasting of the left ventricle. In contrast to CHF patients without cachexia, in whom LV mass tends to increase further over time, patients with cardiac cachexia show a significant decrease of LV mass during follow-up. These findings were demonstrated in vivo using the CMR, which is the most sensitive and reproducible technique for LV mass estimation currently available [11], and significantly superior to 2D echocardiography [12]. Our sample size calculation shows that we used a sufficiently large patient population to demonstrate significant change in LV mass, and CMR has thus proven to be more sensitive to remodelling changes compared to our previously published results with 2D echocardiography [5]. Changes in LV mass, either up or down, should be considered as part of the natural history of the CHF syndrome, and these changes might suggest different pathophysiological mechanisms to be operative in patients at different stages of their disease.

It is generally accepted that worsening of heart failure is associated with ventricular remodelling and increasing LV mass [7], and this is confirmed in our non-cachectic subgroup of patients. Whether this can be expanded to cachectic heart failure has not previously been investigated. In our study, no significant differences in LV mass were found between cachectic and non-cachectic patients at baseline. However, when monitoring these patients, significant difference in changes in this variable over time were noticed. A possible explanation for these findings is that the patients were analysed at the time when non-cachectic patients on average were still increasing LV mass and cachectic patients were on average losing LV mass.

A number of possible mechanisms might underlie the reduction of LV mass in heart failure patients with cardiac cachexia. It is now commonly recognized that progressive LV dysfunction occurs, in part, as a result of apoptosis [13,14]. The importance of this type of cell death in cardiac failure is not yet firmly established. Questions remain as to whether apoptosis is a cause or a consequence of heart failure. Apoptosis was shown to be associated with the increased myocardial stretch in pressure-overload-induced hypertrophy [15] and to occur at an increased rate and after injury due to ischemia or reperfusion [14,16]. Other well-known triggers of apoptosis include cytokines, oxidative stress and mitochondrial damage [17,18]. Patients with severe CHF and particularly with cachexia have been shown to have high circulating levels of tumour necrosis factor [19] and other inflammatory cytokines [20]. Tumour necrosis factor causes many of the clinical features of cachexia, and its production is increased in patients with a variety of neoplastic, infective and collagen disorders characterised by muscle wasting and malnutrition [21]. TNF is expressed in the heart of patients with severe heart failure [22]. Apoptosis may result, and this could explain the reduction in LV mass in cachectic CHF patients.

Different loading conditions, particularly left atrial pressure and LV afterload, might conceivably be involved in the changes in LV cavity size and mass over time. Underfilling of the ventricle or an increase in left atrial pressure, possibly as the result of inappropriate diuretic therapy, might cause changes in LV cavity size [23]. Decreased LV afterload was associated with a reduction in LV mass in an echocardiographic study of anorexia nervosa [24]. In our study, the reduction in LV mass in cachectic patients was not associated with any changes in LV dimensions and ejection fraction. The blood pressure was also similar in the two study groups at baseline, and did not change significantly during follow-up.

Remodeling of the ventricle, clinically manifested as changes in size, shape and function of the heart after cardiac injury [25], is another important mechanism underlying the progression of heart failure [26]. It is a process that is common to multiple heart failure etiologics [27], which can be delayed or even reversed by appropriate treatment [28,29]. Our patients were on stable therapy and there were no significant differences in medication between the two groups. The reduction in LV mass in the cachectic group was not accompanied with a similar reduction in the ventricular cavity size, thus further decreasing the LV mass to volume ratio and further distorting the overall geometry of the ventricle, which is an independent prognostic marker in these patients [30].

4.1. Study limitations

The individual measurements we made in LV cavity size and mass will have been subject to measurement error, a problem compounded when small differences between those made on two occasions several months apart were derived. To minimise this effect, identical equipment and standard guidelines were used on both occasions, and all the images were analysed by the same investigator, blinded to the clinical details of the patient and the CMR study date. The LVEF appears to be relatively high in the patients studied here, but it has been recognised that CMR generally derives higher (and more accurate) LVEFs than echocardiography [31]. Indeed, the LVEF by radionuclide ventriculography was available in seven (of nine) cachectic and in 26 (of 28) non-cachectic CHF patients included into this

study and averaged 30 ± 10% and 33 ± 16% in the cachectic and non-cachectic subgroups, respectively ($P=0.49$). Although all patients were on standard medications, treatment was individualised and was thus not uniform throughout the group of patients studied. Finally, measurements in individual patients were made on only two occasions, so we cannot say whether these changes are consistent or subject to longer term variability in their direction or magnitude. However our study is supported by our previously published echocardiography follow-up study [5].

5. Conclusions

The direction of changes over time in LV mass differs in CHF patients with cachexia as compared to those without cachexia. A significant decrease in LV mass occurs in patients with cardiac cachexia. This study documents in vivo the occurrence of wasting of the left ventricle in patients with CHF who demonstrate general body wasting. Further studies are needed to find out the mechanisms of cardiac wasting in these patients.

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